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Systolic Mechanical Properties of the Left Ventricle

Effects of Volume and Contractile State

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SUMMARY. To characterize the mechanical properties of the contracting left ventricle, we studied the changes in left ventricular systolic pressure following step-like perturbations (± 3 ml) in ventricular volume, using an isovolumically beating, isolated canine heart preparation. Three mechanical properties (elasticity, resistance, and a deactivation effect) were identified. The elastic property differs from the traditional parallel and series elastic elements; it is a time-varying elasticity that includes active and passive effects of volume changes. Furthermore, it could not be represented by a simple time-varying elasticity, but required a second factor to express the dependence of end-systolic elasticity on the timing of the volume step. This effect was represented by a "volume influence factor," which may arise from length-dependent activation. The resistive property appeared to be related to force-velocity behavior of the myocardium. Each mechanical property reacted characteristically to steady state changes in ventricular filling volume or contractile state produced by dobutamine (2–13 $\mu\text{g}/\text{min}$). Our findings indicate that elasticity was the property most sensitive to changes in contractile state; these changes increased peak isovolumetric pressure 54% on average, and raised elastic stiffness 40% above control (which was 5.1 mm Hg/ml). Changes in ventricular filling volume only prolonged, but did not alter, the level of elastic stiffness attained at peak pressure. These results support the view that elasticity—or the end-systolic pressure-volume relationship—serves in a given heart to quantify contractility. The "volume influence factor" was not affected by either filling volume or contractile state. Resistance increased in direct proportion with ventricular pressure, but this linear relation was not altered greatly by changes in contractile state or in ventricular filling volume. At 100 mm Hg, ventricular resistance averaged 0.11 mm Hg/ml per sec. Finally, deactivation was greater the later in systole a volume step was imposed, and this pattern was independent of changes in ventricular filling volume and in contractile state. (*Circ Res* 52: 319–327, 1983)

TO STUDY and quantify the "internal mechanical condition" of the myocardium—in particular, the net resultant of myocardial function which is expressed by the left ventricle—we have applied the method of step responses to the left ventricle as a whole. This method was first applied to muscular tissue by Gasser and Hill (1924), who believed that "the chief means at our disposal for investigating the internal mechanical condition of muscle is that of the quick release or the sudden stretch." More recently, Huxley and Simmons (1971) have demonstrated the continued utility of step responses for illuminating the mechanical nature of contraction. Encouraged by this background, but taking care to minimize the potentially destructive influence of rapid perturbations (Bodem and Sonnenblick, 1974), we applied step-like changes in ventricular volume to an otherwise isovolumic ventricle and observed the resulting changes in ventricular pressure (Hunter et al., 1979).

The results of a series of volume steps (each imposed at a different phase of systole) are a complex set of pressure responses. However, this seemingly complex picture can be simplified by separating each measured response into individual contributions from an elastic property, a viscous property, and a deacti-

vating effect. Here it should be emphasized that the elastic property we measure is not the same as either the parallel or series elastic component, both of which have been used traditionally in muscle mechanics. Our use of the terms elasticity, viscosity, and deactivation will be explained in the next section.

In a previous report (Hunter et al., 1979), it was suggested that these three components could be used to interpret the measured responses to volume steps. In the present report, we describe a quantitative method to calculate these mechanical components and then investigate the way in which the derived components are influenced by changes in ventricular volume and myocardial contractility.

Definition of Mechanical Components

Elastic Property

Our definition of the elastic property includes both the active and passive effects of a volume change. Actively developed elasticity is related to the Frank-Starling mechanism. For instance, after a step increase in volume at the beginning of contraction, the left ventricle will generate more pressure, and this increase in developed pressure (per unit volume in-

fused) appears as an elastic component. We have retained the term elastic to describe this component because, mechanically speaking, one uses an elastic element to express a relation between pressure and volume. This view of active elasticity is similar in concept to the elastic property implicit in Suga and Sagawa's (1974) time-varying pressure:volume ratio.

Because it includes actively developed pressure, the elastic property is related in some way to the activation of the myofilaments. In the simplest case, developed pressure might be thought to be the product of two influences: (1) the level of activation and (2) ventricular volume. Because active elasticity expresses the ratio of developed pressure to volume, the value of elastic stiffness might possibly be used as a measure of activation. Although our results indicate that this reasoning is oversimplified, it does serve to indicate the close connection between active elasticity and activation.

In the view of active elasticity just presented, volume and activation would be mutually independent determinants of developed pressure. For the experiments we performed, therefore, one would expect that the same size volume step would produce the same change in end-systolic pressure— independent of whether the volume step was applied just before activation began, in the middle of the activation process, or even near its conclusion. However, this prediction was not borne out by our previous results (Hunter et al., 1979). The later in systole a volume step was imposed, the less influence it exerted on peak ventricular pressure. Thus, the picture of active elasticity that emerged from these experiments was more complex than a simple time-varying elastance model would suggest. The complications may reside in an interaction between activation and volume, such as length-dependent activation in cardiac muscle. That these observations are potentially consistent with length-dependent activation is outlined in the Discussion.

We have attempted to quantify this more complex phenomenon by including two factors to describe the relationship between pressure and volume for the elastic property. The first factor is a time-varying elastance, $E(t)$, similar in concept to that described by Suga and Sagawa (1974). The second factor we have called the "volume influence factor," $B(T)$. It embodies our observation that the time in systole at which a volume step occurs is also an influence on the resulting pressure. To summarize in an equation:

$$\Delta P(t)_{\text{elastic}} = E(t) B(T) \Delta V(T). \quad (1)$$

$\Delta P(t)_{\text{elastic}}$ indicates the contribution of the elastic property to the pressure response (i.e., change from isovolumic) caused by a volume step, $\Delta V(T)$. T represents the particular time within a beat when a volume step was imposed, and t represents any subsequent time within the same beat. By definition, the influence factor (B) must equal 1 at the start of a contraction (when volume steps exert their largest effect), and it decreases later in systole (when the

elastic component contributes less to pressure changes).

Viscous Property

In hydraulic systems, viscosity describes the influence of flow [$Q(t)$] on pressure. We have also chosen to represent flow-dependent influences on ventricular pressure by a viscous property. However, the major determinant of effective ventricular viscosity is not likely to be the viscosity of blood in the chamber, but the shortening of myocardial fibers which must accompany flow. Thus, one would expect the ventricular viscous property to reflect the force-velocity behavior of cardiac muscle translated to the ventricular level. Instantaneous viscous resistance (R) expresses the decrease in pressure (ΔP) below the isovolumic value as a function of flow during ejection:

$$\Delta P(t)_{\text{viscous}} = R Q(t). \quad (2)$$

Deactivating Effect of Displacement

Sudden displacement of the myofilaments during contraction has been shown to cause irrecoverable loss of contractile force during that beat (Brady, 1965; Bodem and Sonnenblick, 1974). This phenomenon also contributed to the responses in our study. However, we avoided placing unnatural overemphasis on this factor by restricting the maximum velocity and frequency content of the flow pulses (which accompany the volume steps) to the range found in normal physiological conditions (i.e., maximum flow < 100 ml/sec; 90% of energy in flow pulse < 20 Hz). For the small volume steps we imposed (≤ 3 ml), the deactivation component [$D_T(t)$] could be represented by:

$$\Delta P(t)_{\text{deactivation}} = -D_T(t) |\Delta V(T)|. \quad (3)$$

The absolute value of ΔV indicates that the deactivating effect occurred both for infusions and withdrawals of volume. In either case, its effect was always to reduce ventricular pressure (hence, a negative sign). $D_T(t)$ represents the normalized time course (function of t) of the deactivation component for a volume step imposed at time T . One might also expect deactivation to be smaller for less rapid volume "steps" than those we usually applied, and our results confirm this. However, the dependence of deactivation on velocity will not be analyzed in this report, which emphasizes changes in elastic and viscous properties.

The total response in pressure to the imposed volume steps is the sum of these three components. Normalizing for the size of the volume step:

$$(\Delta P/\Delta V)_{\text{total}} = E(t) B(T) + R Q(t)/\Delta V - \delta D_T(t) \quad (4)$$

where $\delta = +1$ for infusion and -1 for withdrawal.

Methods

Physiological Preparation

We used isolated canine hearts which contracted isovolumetrically, except for the step-like perturbation in volume produced by a flow pulse. These isolated hearts were metabolically supported by cross-circulation with an anesthe-

tized dog. All dogs were anesthetized with sodium pentobarbital (20–40 mg/kg, iv), and anesthesia was maintained by supplemental doses. The details of the preparation have been described fully elsewhere (Janicki et al., 1974). Briefly, the hearts were paced from electrodes attached to the right atrium, the pericardium remained intact, and the right ventricle was vented and, thus, generated no pressure. A compliant latex balloon was positioned in the left ventricular cavity through the mitral orifice. The balloon was coupled to a cylinder with a piston, and the volume in the balloon was controlled by an electrohydraulic actuator. Ventricular volume was measured from the position of the piston, and ventricular outflow was measured by an extracorporeal electromagnetic flow probe inserted between the balloon and piston. Left ventricular pressure (LVP) was measured by means of a short Teflon catheter and a Statham transducer (P23Gb).

Experimental Protocols

With the heart in a steady state, the volume of the otherwise isovolumetrically contracting left ventricle was reduced step-wise by 2–3 ml at any chosen time in systole. Outflow was limited to a narrow pulse lasting 40–50 msec. Ventricular pressure during and after this withdrawal was lower than the corresponding pressure in the preceding isovolumetric control beat. The difference in pressure (ΔP) between control and perturbed beats, measured at each instant of contraction, was divided by the total change in volume (ΔV) to give the step response ($\Delta P/\Delta V$). Only one test step was applied in any contraction, and at least 6 seconds elapsed between perturbed beats. To generate a complete set of responses, a series of 8–10 volume steps were imposed, with each successive step coming 20 msec later in systole. Representative responses are given in Figure 1 for steps applied early in systole, in mid-systole, and at the time of peak pressure. The direction of volume steps

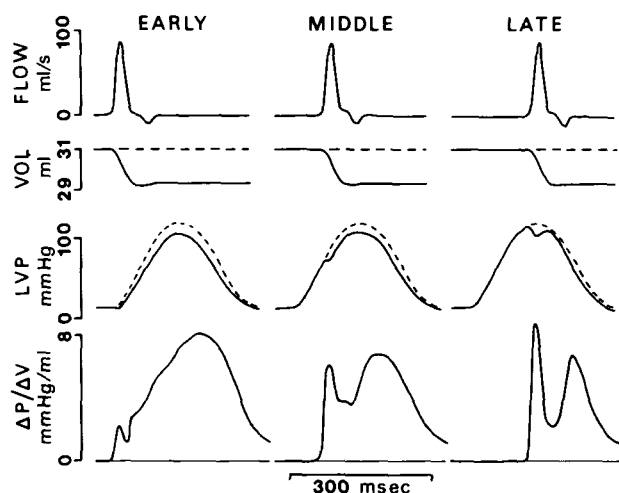


FIGURE 1. Examples of the experimentally imposed flow and volume perturbations and the ventricular pressure responses. The dashed lines show control left ventricular pressure (LVP) when chamber volume (VOL) was held constant. The step response itself ($\Delta P/\Delta V$) was calculated by taking the instantaneous difference in pressure produced by a volume step (i.e., the difference between solid and dashed lines in LVP tracings), and dividing it by the difference in volume (ΔV) between the two levels. Steps were imposed at various phases of systole (e.g., early, middle, late). Data from experiment 6. In this and the next two figures, data were retraced from computer-generated graphics.

could be reversed (i.e., adding volume to the ventricle) to produce a complementary set of responses. The notation $(\Delta P/\Delta V)_w$ and $(\Delta P/\Delta V)_i$ will be used to differentiate responses measured during withdrawals and infusions, respectively. Additional details of the perturbation protocol can be found in an earlier report (Hunter et al., 1979).

After completing a set of step-like withdrawals and infusions of volume, we altered the steady state conditions of contraction. Either ventricular volume was shifted to a new level (range = 15–54 ml; EDP = 4–20 mm Hg) or dobutamine was infused (2.15–13.2 $\mu\text{g}/\text{min}$). We judged the steady state during a set of perturbations by the constancy of peak LVP. The median standard deviation within a data set was typically ± 2 mm Hg.

The heart was paced at a rate sufficient to override the basal sinus rhythm and the chronotropic effects of dobutamine. Thus, heart rate was held constant throughout, even when dobutamine was not being infused. Because dobutamine has only modest chronotropic effects in the dose range used, these rates were not excessive (range = 120–160 beats/min).

Data Analysis

First, we separated the deactivation component (D) from the elastic (E) and viscous (R) components. Because of the approximate directional symmetry of the E and R components, as suggested by our previous observations (Hunter et al., 1979), their contribution to $(\Delta P/\Delta V)$ would be nearly identical for both withdrawal and infusion. In withdrawal, ΔV and ΔP are both negative; during infusion, they are both positive. Consequently, the $\Delta P/\Delta V$ ratio should not depend on the direction of perturbation. Thus, we assumed that any difference between $(\Delta P/\Delta V)_w$ and $(\Delta P/\Delta V)_i$ would be due to the deactivation component (D). D was set equal to one half this difference. On the other hand, by taking the average of $(\Delta P/\Delta V)_w$ and $(\Delta P/\Delta V)_i$, the deactivation component (D) would be cancelled; hence, we assumed that the average response $[(\Delta P/\Delta V)_{\text{avg}}]$ represented the combination of elastic and resistive components by themselves.

The separation of the deactivation component (D) from the combined E and R components could be complicated by differences between infusion and withdrawal in the form of the flow perturbation. Only slight differences were encountered in practice, and our calculations of D, E, and R were refined accordingly.

The elastic and resistive components could be separated from each other because the perturbation method constrained flow to a short time interval. Once the flow pulse had ceased, any resistive effect would be zero and only the elastic effect, due to the change in volume, would continue to contribute to $(\Delta P/\Delta V)_{\text{avg}}$. Thus, the elastic component of the step response $[E(t) B(T) \text{ in Eq. 4}]$ could be directly equated to $(\Delta P/\Delta V)_{\text{avg}}$ for the remainder of the beat after the perturbation flow had returned to zero.

By definition, $B(T)$ equals 1 for steps applied at end-diastole or early in systole, so that $E(t)$ could be equated to $(\Delta P/\Delta V)_{\text{avg}}$ obtained from the earliest volume step. $E(t)$ was also filtered to remove small oscillations in $\Delta P/\Delta V$ caused by oscillations in flow following the main pulse (Fig. 1). The digital filter allowed frequencies up to 8 Hz to pass nearly undistorted (delay < 2 msec, magnitude within 2%); beyond 8 Hz, attenuation increased sharply (e.g., at 24 Hz only 5% of the input remained).

We computed the volume influence factor, $B(T)$, by taking the ratio of the elastic component of the response observed following a particular volume step (imposed at time T) to that observed following the earliest volume step

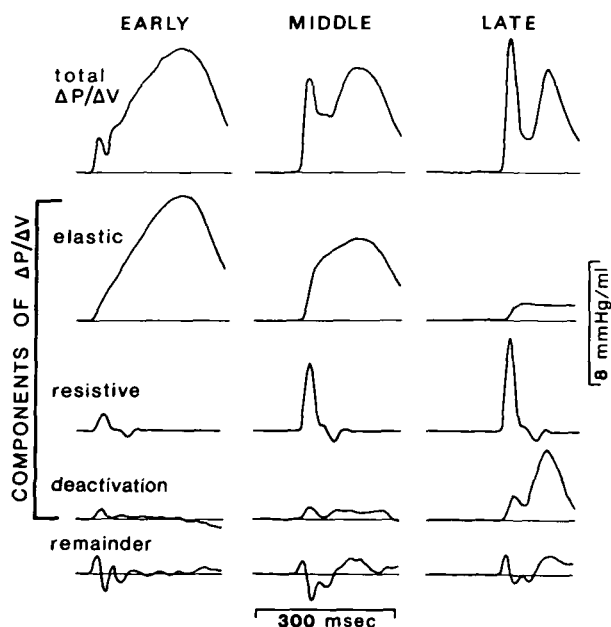


FIGURE 2. In each column, the total step response (top) corresponding to the data shown in Figure 1 has been resolved into its elastic, resistive, and deactivation components. The sum of these components closely approximated the contour of the step response, and only a small remainder (bottom) was required to reproduce the measured step response exactly. As the timing of the volume step was delayed from early (left) to middle and late systole (right), the elastic component progressively decreased while the resistive and deactivation components increased. An associated set of data from infusions (not shown) was also examined to enable calculation of these components.

(i.e., $E(t)$ as described above). We evaluated this ratio at one representative time (the time of peak ventricular pressure), and assumed that the ratio would be constant throughout the response to a step.

Once the pattern of elasticity had been established, the internal resistance of the ventricle could be computed. Resistance contributed to the pressure response only during the narrow flow pulse. Because elasticity also produced changes in pressure during this flow pulse, the resistive component of $\Delta P/\Delta V$ was set equal to the difference between the measured $(\Delta P/\Delta V)_{avg}$ and the instantaneous contribution from the elastic component. Resistance equaled the resistive component of $(\Delta P/\Delta V)$ divided by $(Q/\Delta V)$ (see Eq. 4). We elected to compute this ratio at the time of peak flow, when the resistive contribution to ΔP would be maximal. Thus, from each flow pulse, we obtained information

about resistance at one particular phase of systole; analyzing the resistive response to pulses inserted at all phases of systole then gave a complete picture of the variation in resistance during contraction.

Figure 2 shows the elastic, resistive, and deactivation components derived from the set of step responses presented in Figure 1. The relative contribution of each component to the total response altered continuously as the volume step was applied later in systole.

Verification of Components

To verify that the derived components adequately represented the measured step responses, we calculated the difference between the measured response and the sum of components (Eq. 4). This difference was called the remainder.

The calculation from components incorporated two of the general results which are presented later: (1) beyond a breakpoint (see Fig. 5), $B(T)$ decreased linearly with time, and (2) R varied linearly with LVP. These linear relationships were determined by regression analysis of individual measurements from the variously timed volume steps. The regression relations then were used to calculate the response $(\Delta P/\Delta V)$ according to Equation 4. Note that the expression for the elastic component (first term in Eq. 4) had to be expanded so that it would also apply during a flow pulse, when volume was changing: $\int E(t) B(T) Q(T) dT/\Delta V$. Also note that we assumed there would be a minimal value of elasticity equal to the passive diastolic stiffness, estimated from the value of $(\Delta P/\Delta V)_{avg}$ at the end of relaxation.

Typical examples of the remainder are shown in Figure 2. On average, the remainder was less than 10% of the average measured response. There was a trend for remainders to have larger relative magnitudes for steps imposed later in systole.

As a qualitative verification, we also studied how the speed of volume changes affected the components of response. As would be expected for an elastic property, halving the speed of the volume step did not change either $E(t)$ or $B(T)$, so long as the mid-point of the volume step occurred at identical times in systole. Both the resistive and deactivation components were smaller with slower steps, and these decreases are also expected from the nature of these components.

Results

Table 1 gives the basal conditions at the onset of data collection for the six isolated hearts studied. Also shown are the magnitude of the elastic, resistive, and deactivation components in the basal state. With a change in contractile state or end-diastolic volume,

TABLE 1
Basal Conditions

| Experiment no. | LV mass (g) | Pacing rate (beats/min) | LVP syst/diast (mm Hg) | LV volume (ml) | Elasticity at peak LVP (mm Hg/ml) | Resistance at 100 mm Hg (mm Hg/ml per sec) | Deactivation (max value) (mm Hg/ml) |
|----------------|-------------|-------------------------|------------------------|----------------|-----------------------------------|--|-------------------------------------|
| 1 | 90 | 130 | 88/12 | 37 | 5.1 | 0.12 | 2.6 |
| 2 | 140 | 160 | 64/11 | 45 | 4.4 | 0.11 | 2.9 |
| 3 | 107 | 133 | 103/9 | 37 | 6.8 | 0.08 | 3.4 |
| 4 | 119 | 140 | 130/10 | 34 | 7.1 | 0.10 | 4.2 |
| 5 | 101 | 150 | 84/7 | 30 | 5.3 | 0.11 | 2.7 |
| 6 | 97 | 120 | 83/10 | 23 | 6.0 | 0.13 | 3.5 |

LV = left ventricle, LVP = systolic/diastolic pressure.

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the step responses altered in a predictable manner, and the qualitative pattern of responses was not affected (for an example, see Fig. 6, Hunter et al., 1979). Thus, the decomposition of responses using the defined set of mechanical components worked equally well under all conditions. The behavior of each component will now be described in detail.

Elastic Component

With increases in ventricular volume, the time course of the basic elastic component $E(t)$ was primarily prolonged (Fig. 3), but its initial rise was not altered. At high volumes (EDV > 12 mm Hg), increases in diastolic stiffness could be discerned in the levels of $\Delta P/\Delta V$ reached at the end of relaxation. On the other hand, increasing the inotropic state caused $E(t)$ to rise more quickly and to peak at a higher level, while the duration remained constant or shortened slightly.

To quantify changes in the amplitude of $E(t)$ in a way that would facilitate comparison with changes in ventricular pressure (LVP), we selected the value of $\Delta P/\Delta V$ at the time of peak LVP (as indicated by the vertical bars in Fig. 3). The difference in elastic response between changes in volume and contractility is evident in Figure 4. The open circles represent the effect of increasing volume (no change in E , $P > 0.7$), whereas the closed circles show the effect of dobutamine ($P < 0.001$). Note that dobutamine did not always act equally on elasticity and LVP; in several cases, the increase in elastic stiffness was proportionally less than the increase in peak ventricular pressure.

The volume influence factor (B) was not altered significantly by changes in either ventricular volume or contractile state. An example of the lack of variation in B among all the cases studied in one heart is

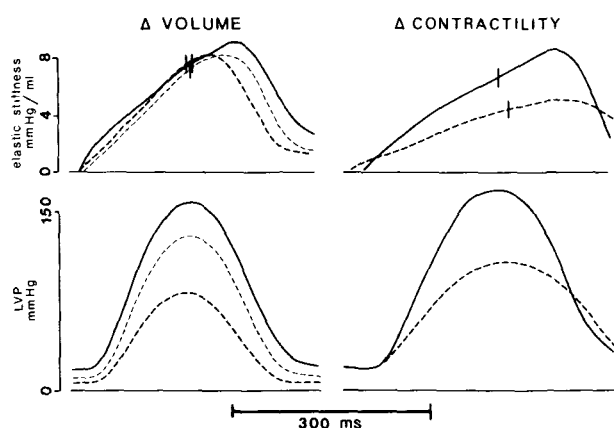


FIGURE 3. Changes in ventricular volume (left) and myocardial contractility (right) alter the time course of elastic stiffness in characteristically different ways, although both increase isovolumetric ventricular pressure (LVP, bottom). Vertical bars crossing the stiffness tracings indicate the time of peak LVP. Left panel: volumes = 23 ml (heavy dashed line), 34 ml (light dashed line), and 42.5 ml (solid line); no dobutamine (expt. 4). Right panel: changes produced when dobutamine was infused at 6.6 $\mu\text{g}/\text{min}$ (solid line); volume held constant at 45.5 ml (data from experiment 1).

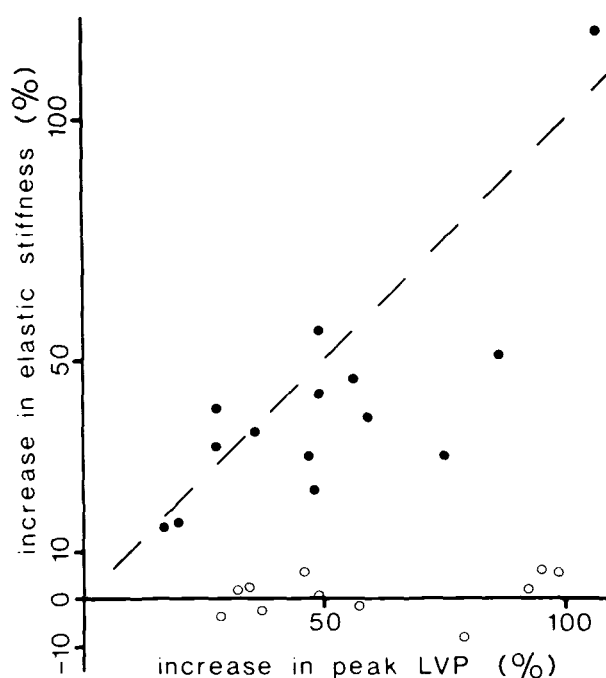


FIGURE 4. The percent increase in elastic stiffness is compared to the percent increase in peak isovolumetric left ventricular pressure (LVP). When the rise in pressure occurs with increases in ventricular volume (○), elasticity does not change. With increases in contractility (●) elastic stiffness rises, often—but not always—in proportion to the increase in LVP (i.e., along the line of identity, drawn dashed). Data pooled from all experiments.

presented in Figure 5. The time of the volume step (i.e., time at peak flow) was expressed as a fraction (phase) of the systolic period. Volume steps imposed at early phases of systole exerted their full influence on pressure ($B = 1$). At an average phase of $0.26 \pm$

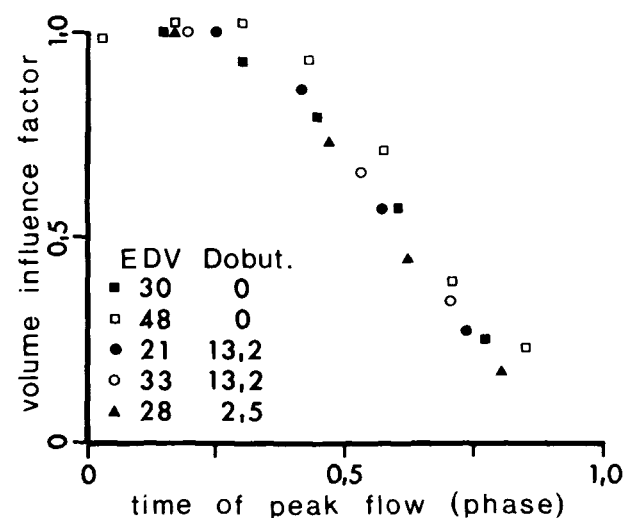


FIGURE 5. Progressive decrease of the volume influence factor when volume steps were applied at progressively later phases of systole. Phase represents a normalized time: phase = 0 at the onset of systole; phase = 1 at the time of peak pressure. Different symbols correspond to different combinations of ventricular volume (EDV, ml) and dobutamine infusion (Dobut., $\mu\text{g}/\text{ml}$) (data from experiment 5).

0.07 sd, there was a breakpoint, beyond which the "elastic" influence of volume steps decreased in a linear fashion. Extrapolating the trend of this decrease, B would have reached the value zero at an average phase of 1.05 ± 0.10 sd (i.e., just beyond the time of peak pressure).

Internal Resistance

During contraction, the internal resistance (R) increased in parallel with ventricular pressure (LVP). Therefore, we plotted R vs. the isovolumetric LVP at the time of measuring R (which was the time of peak flow). We found an essentially linear relationship ($r > 0.92$ for all cases), as illustrated in Figure 6. R increased with LVP at an average rate of 0.107 mm Hg/ml per sec per 100 mm Hg (range for all hearts: 0.076 to 0.134). The intercept of R at zero LVP usually was near zero (range: -0.013 to $+0.011$ mm Hg/ml per sec).

Changes in contractile state did not significantly ($P > 0.1$) alter the relationship between ventricular pressure and internal resistance. Figure 6A shows one example out of 14 comparisons. Maximum resistance was larger following an infusion of dobutamine (circles), but the increase in resistance followed the same linear regression as in the case without dobutamine. The intercept of resistance at zero pressure also did not change significantly. Statistical significance was judged by the paired *t*-test for two regression lines (Brownlee, 1965).

Changing ventricular volume, on the other hand, could alter the relation between ventricular pressure and internal resistance, although only slightly. As seen in Figure 6B, increasing volume (triangles) rotated the relation downward and to the right so that the internal resistance at an equivalent pressure was lower. A decrease in the slope of the R vs. LVP relation occurred in all 12 instances in which ventricular end-diastolic volume was increased. However, this decrease in slope was statistically significant only

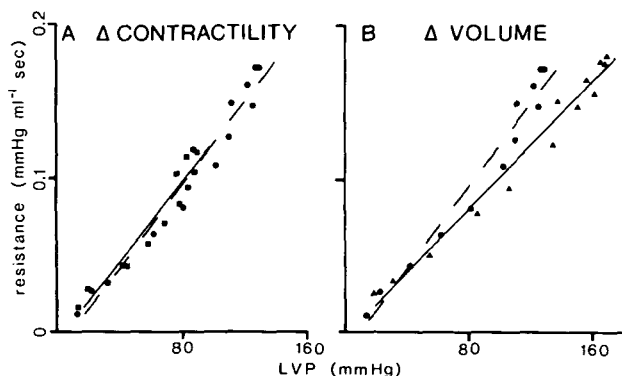


FIGURE 6. Influence of changes in contractility or volume on the linear relation between ventricular pressure (LVP) and resistance. The solid or dashed line is the regression line for each condition. Left panel: beginning from a control contractile state (■), dobutamine was infused at $6.6 \mu\text{g}/\text{min}$ (●); volume was constant at 36 ml. Right panel: chamber volume was increased from 36 ml (●) to 46 ml (▲), while dobutamine infusion was maintained at $6.6 \mu\text{g}/\text{min}$ (data from experiment 1).

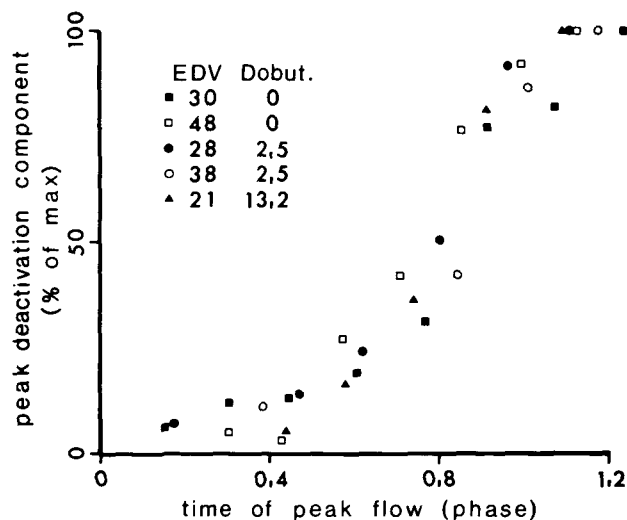


FIGURE 7. The peak value of the deactivation component increased continuously as volume steps were applied at successively later phases of systole. Phase = 0 at onset of systole; phase = 1 at time of peak pressure. Deactivation components are expressed as a percent of the largest one found under a given condition of volume and contractile state. Each symbol represents a different combination of volume (EDV, ml) and dobutamine infusion (Dobut., $\mu\text{g}/\text{min}$) (data from experiment 5).

for large changes in volume (i.e., $\Delta\text{EDV} > 13$ ml). The resistance at zero pressure (y-intercept) in all but two cases was unaffected by alterations in volume.

Deactivation Component

Variations in the time course of the deactivation component following volume steps inserted at three phases of systole were shown in Figure 2. The largest decrease in pressure attributed to deactivation (D) occurred when a step was imposed late in systole (right panel). This maximum was not synchronous with the flow pulse; instead, D peaked during the relaxation phase within 10 msec of peak negative dP/dt . There was also a secondary, smaller peak in D located more in synchrony with the flow pulse. For volume steps inserted earlier in systole (middle and left panels), D was progressively smaller and became negligible for the earliest steps. The trend for growth in D as systole progressed is summarized in Figure 7.

The tendency of the deactivation component to increase as volume steps were applied later in systole remained unaltered when either ventricular volume or contractile state were changed (Fig. 7). On the other hand, the absolute magnitude of D did rise with increasing volume or contractile state. The increase ranged from 2% to 57% but correlated poorly ($r < 0.4$) with the percent increase in peak LVP.

Discussion

This report quantitatively substantiates our previous hypothesis (Hunter et al., 1979) that the systolic mechanical properties of the left ventricle, as revealed by step-response tests, can be adequately described by three mechanical components: elasticity, resist-

ance, and deactivation. The elastic component displays a complex behavior, so two time-varying parameters have been used to represent it [$E(t)$ and $B(T)$ in Eq. 1].

As we altered end-diastolic volume and contractile state, ventricular elasticity and resistance each changed in a characteristic manner. The component most sensitive to changes in contractile state was elasticity. This finding thus supports the use of pressure-volume relations as indicators of myocardial contractile strength (Sagawa, 1978). Resistance (R) also increased with catecholamine infusion, but the increase appeared to depend on the increase in LVP rather than a shift in the relation between R and LVP. In contrast to alterations in contractile state, variations in ventricular volume did not affect the mechanical components as dramatically. Elasticity (observed at peak LVP) was essentially unchanged, and the relation between R and LVP shifted only slightly to lower resistances. These general conclusions about ventricular mechanical properties must be tempered, however, by the fact that we confined these observations to volume perturbations of ± 3 ml about the isovolumetric state.

Critique of Method to Derive Mechanical Components

We checked whether the three mechanical components could reproduce the total measured pulse response, and there was always a close fit, even under widely varying physiological conditions. Any additional mechanical effects, such as inertia (Tallarida, 1970; Templeton and Nardizzi, 1974) or series elasticity (Covell et al., 1975; Schiereck and Boom, 1978) appeared to have negligible influence. For example, although the initial oscillations of the remainders shown in Figure 2 suggest an inertial effect, the peak amplitude of such brief oscillations averaged only 0.84 mm Hg/ml, even for the magnitude of acceleration present in the flow pulses.

The procedure to separate the step responses into components employed several simplifying assumptions: (1) The elastic and resistive components should act symmetrically with respect to the direction of volume change—that is, the pressure decrease they produce following a withdrawal should match (in magnitude) the pressure increase for an infusion of the same amount. This assumption is more likely to be satisfied for the small volume perturbations we studied than for larger volume changes. (2) The pressure decrease related to deactivation should be due to the displacement itself—independent of whether volume was infused or withdrawn. (3) The elastic component of response to steps applied later in systole should follow the same *relative* time course as the elastic components for early steps. With this constraint, the variation in the elastic component between early and late volume steps can be described adequately by a single variable (the “volume influence factor”). These three simplifications may not be exactly fulfilled in practice, and deviations from them

probably contributed to the residual component of response (the remainder in Fig. 2) that was not explained by the three components. Nevertheless, the small magnitude of the remainders suggests that the assumptions are practical and useful. Deviations from the first two assumptions could also have caused a portion of the response to be misassigned to deactivation instead of the other components (or vice versa). However, the deactivation we found did behave similarly to that described for cardiac muscle (Brady, 1965; Kaufmann et al., 1972) in being more prominent the later in systole that displacement occurred.

Comparison with Other Measurements

Despite the different methods employed, the influence of end-diastolic volume and myocardial contractile state on ventricular elastic stiffness [$E(t)$] was similar to the behavior of the pressure:volume ratio (P/V) reported by Suga et al. (1973, 1974). When measured at the time of peak ventricular pressure, both E and P/V were larger following catecholamine infusion and unchanged following shifts in end-diastolic volume. However, in the experiments of Suga et al., the percent increase in P/V with contractile state would match the percent increase in peak LVP [because the volume intercept (V_d) was constant]; in our data, the increase in E was not always as large as the increase in LVP. An additional difference between the P/V behavior and our results is our observation of a “volume influence factor” [$B(T)$]. This phenomenon has not been reported by other investigators.

Similar to the resistive component reported here, the viscous element studied by Templeton et al. (1972, 1974) also varied linearly with ventricular pressure, and the pressure-viscosity relationships were just extended and not altered by catecholamine stimulation or changes in ventricular volume. In severely depressed hearts, however, Templeton et al. (1975) reported that viscosity at each level of LVP was increased. Qualitatively, the phenomenon expressed by Templeton’s viscous component appears similar to the resistance we observed. However, a quantitative comparison is limited because different models were used to derive the components.

Rather than observing the variation of mechanical properties during systole, Elzinga and Westerhof (1974, 1978) examined the mean internal impedance of the ventricle averaged over the cardiac cycle. Thus, their average impedance does not measure the same entity as the instantaneous resistance described by us; instead, average impedance appears to be associated with the time integral of ventricular elastance (Westerhof and Elzinga, 1978). Both systolic elastance and average impedance are increased by inotropic stimuli, and both remain nearly constant during changes in end-diastolic volume.

The elasticity we measured should not be equated with the effective ventricular “series elasticity” measured by others following abrupt volume steps in the ventricle (Covell et al., 1975; Schiereck and Boom, 1978) or, similarly, by rapid length steps in cardiac

muscle (Brady et al., 1981). Changes in series elastic stiffness during contraction apparently did not contribute directly to the responses we measured. For example, had series elasticity exerted a significant direct influence, the initial transient pressure response would have continued noticeably beyond the time of the volume step and its flow pulse. Instead, we found the flow pulse and the associated pressure transient to be practically in phase. Only by increasing the speed of the volume change beyond the physiological frequency range [e.g., step complete in 7 msec (Schierreck and Boom, 1978)] can a distinct series elastic property be clearly demonstrated. For slower volume changes (i.e., within the physiological range), any "series elastic element" appears to have a small enough compliance that it can be neglected as a separate component (although it may slightly modify the measured E and R components).

Comparison with Cardiac Muscle

The dominant mechanical properties of the isovolumetrically contracting ventricle are elasticity and resistance. These are analogous to two dominant mechanical characteristics of cardiac muscle: the force-length and force-velocity relations (Brutsaert and Paulus, 1977; Weber and Janicki, 1977). The third mechanical phenomenon observed in the ventricle also has its counterpart in muscle mechanics: deactivation caused by a length change (Brady, 1965; Kaufmann et al., 1972). This similarity between the intact ventricle and isolated muscle encouraged us to seek explanations for the behavior of the ventricle in terms of phenomena observed with cardiac muscle. Whereas the shape of the ventricle and orientation of muscle fibers must also be considered when transforming the behavior of isolated muscle to the whole ventricle, it is difficult to explain our findings through this mechanism. For example, one would expect the shape of an isovolumetric ventricle to change primarily during the transition from its resting to active configurations in the early phases of systole (Olsen et al., 1981). During this time, however, the response to volume steps was nearly independent of when the step was imposed (Hunter et al., 1979).

That ventricular resistance increases linearly with isovolumic ventricular pressure may reflect the nature of the force-velocity relation. Hill's equation (Hill, 1938) can be arranged to a form demonstrating explicitly that internal muscle resistance increases in proportion to force (Brady, 1965): $(F_0 - F)/v = (1/b) \times F + (a/b)$ [a, b are Hill's constants]. The left side of this equation defines the internal resistance of a muscle fiber in a manner analogous to our definition of resistance for the ventricle; i.e., the difference in force between shortening (F) and isometric contractions (F_0) divided by the velocity of shortening (v). Although Hill's equation applies to steady state shortening under tonic activation (a different situation than our experiment), the underlying basis of the phenomena may be similar. In muscle, the linear relation between resistance and force may arise from the summated action of a large number of independent subcellular

force generators (Huxley, 1957). If each force generator acted, on the average, as if it had an inherent "resistance" (i.e., it generated less force when shortening faster), then total resistance and total force would increase in proportion as more force generators became active.

The slope of the relation between resistance and pressure in the ventricle reflects an inherent dependence on velocity within the contractile machinery. Note that the dimension of this slope (s/ml) is inversely related to the velocity of shortening. Geometrical factors may explain the slight decrease in slope at larger ventricular volumes, because the same flow rate may be attained with a slower velocity of fiber shortening when the ventricle contracts from a larger volume. On the other hand, when volume was held constant and a catecholamine was infused, it appeared that the intrinsic rate of the contractile reaction was not altered because the slope of resistance vs. pressure did not change. This observation is consistent with the emerging concept that catecholamines improve contractility primarily by altering excitation-contraction coupling (Stull and Mayer, 1979), and not by increasing the intrinsic rate of the contractile reaction. Thus, the larger velocities of shortening that are found during catecholamine infusion may be the result of a more rapid rise in the number of active force-generating sites, rather than an increase in the velocity at each site.

An unusual feature of the elastic behavior of the ventricle was the observation that volume steps applied late in systole caused less change in pressure than the same step applied earlier in systole. This phenomenon would not be expected from the classical concept that the overlap of sliding filaments determines the force-length relation (Braunwald et al., 1976). No matter when a length step occurred, the overlap at end-systole would be equivalent, and one would expect equivalent forces, according to this theory. The inequality in observed forces may possibly be explained by length-dependent reactions in other processes, such as activation (Jewell, 1977). For example, suppose there were decreased activation at shorter lengths. Shortening that occurred after activation was complete, however, would fail to reduce force by this mechanism, and myocardial force would then appear to be less influenced by length changes.

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References

- Bodem R, Sonnenblick EH (1974) Deactivation of contraction by quick releases in the isolated papillary muscle of the cat. Effects of lever damping, caffeine, and tetanization. *Circ Res* 34: 214-225
- Brady AJ (1965) Time and displacement dependence of cardiac contractility: Problems in defining the active state and force-velocity relations. *Fed Proc* 24: 1410-1420
- Brady AJ, Tan ST, Ricchiuti NV (1981) Perturbation measurements of papillary muscle elasticity. *Am J Physiol* 241: H155-H173
- Braunwald E, Ross J Jr, Sonnenblick EH (1976) *Mechanisms of Contraction of Normal and Failing Heart*, ed 2. Boston, Little, Brown & Co, pp 72-87
- Brownlee KA (1965) *Statistical Theory and Methodology in Science and Engineering*. New York, Wiley, pp 349-351
- Brutsaert DL, Paulus WJ (1977) Loading and performance of the heart as a muscle and pump. *Cardiovasc Res* 11: 1-16
- Covell JW, Taylor RR, Sonnenblick EH, Ross J Jr (1975) Series elasticity in the intact heart. *Pfluegers Arch* 357: 225-236
- Elzinga G, Westerhof N (1974) End-diastolic volume and source impedance of the heart. In *The Physiological Basis of Starling's Law of the Heart*. Ciba Foundation 24 (new series). New York, Associated Science Publishers, pp 241-255
- Elzinga G, Westerhof N (1978) The effect of an increase in inotropic state and end-diastolic volume on the pumping ability of the feline left heart. *Circ Res* 42: 620-628
- Gasser HS, Hill AV (1924) The dynamics of muscular contraction. *Proc R Soc Lond [Biol]* 96: 398-437
- Hill AV (1938) The heat of shortening and the dynamic constants of muscle. *Proc R Soc Lond [Biol]* 126: 136-195
- Hunter WC, Janicki JS, Weber KT, Noordergraaf A (1979) Flow-pulse response: A new method for the characterization of ventricular mechanics. *Am J Physiol* 237: H282-H292
- Hunter WC, Janicki JS, Weber KT (1980) Mechanical properties of the ventricle during systole. *Fed Proc* 39: 169-174
- Huxley AF (1957) Muscle structure and theories of contraction. *Prog Biophys Chem* 7: 255-318
- Huxley AF, Simmons RM (1971) Proposed mechanism of force generation in striated muscle. *Nature* 233: 533-538
- Janicki JS, Reeves RC, Weber KT, Donald TC, Walker AA (1974) Application of a pressure servo system developed to study ventricular dynamics. *J Appl Physiol* 37: 736-741
- Jewell BR (1977) A reexamination of the influence of muscle length on myocardial performance. *Circ Res* 40: 221-230
- Kaufmann RL, Bayer RM, Harnasch C (1972) Autoregulation of contractility in the myocardial cell: Displacement as a controlling parameter. *Pfluegers Arch* 332: 96-116
- Olson CO, Rankin JS, Arentzen CE, Ring WS, McHale PA, Anderson RW (1981) The deformational characteristics of the left ventricle in the conscious dog. *Circ Res* 49: 843-855
- Sagawa K (1978) The ventricular pressure-volume diagram revisited. *Circ Res* 43: 677-687
- Schiereck P, Boom HBK (1978) Left ventricular active stiffness: Dependency on time and inotropic state. *Pfluegers Arch* 374: 135-143
- Stull JT, Mayer SE (1979) Biochemical mechanisms of adrenergic and cholinergic regulation of myocardial contractility. In *Handbook of Physiology*, sec 2, Cardiovascular System, vol 1, The Heart. Washington, D.C., American Physiological Society, pp 741-774
- Suga H, Sagawa K (1974) Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circ Res* 35: 117-126
- Suga H, Sagawa K, Shoukas AA (1973) Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res* 32: 314-322
- Tallarida RJ, Rusy BF, Loughnane MH (1970) Left ventricular wall acceleration and the law of Laplace. *Cardiovasc Res* 4: 217-223
- Templeton GH, Nardizzi LR (1974) Elastic and viscous stiffness of the canine left ventricle. *J Appl Physiol* 36: 123-127
- Templeton GH, Ecker RR, Mitchell JH (1972) Left ventricular stiffness during diastole and systole. The influence of changes in volume and inotropic state. *Cardiovasc Res* 6: 95-100
- Templeton GH, Wildenthal K, Willerson JT, Mitchell JH (1975) Influence of acute myocardial depression on left ventricular stiffness and its elastic and viscous components. *J Clin Invest* 56: 278-285
- Weber KT, Janicki JS (1977) Instantaneous force-velocity-length relationships in isolated dog heart. *Am J Physiol* 232: H241-H249
- Westerhof N, Elzinga G (1978) The apparent source resistance of heart and muscle. *Ann Biomed Eng* 6: 16-32

INDEX TERMS: Mechanical properties • Ventricular mechanics • Canine isolated heart • Ventricular internal resistance • Ventricular systolic elastance • Dobutamine